REMARKS

Claims 103-144 are pending in the present application. For the Examiner's convenience, an Appendix containing these claims is attached hereto.

Applicants respectfully request reconsideration and withdrawal of the final rejection of claims 103-144 based on the following remarks and supporting evidence submitted herewith as Appendices A and B.

Rejection of Claim 133, Under 35 USC §112, Second Paragraph

Claim 133 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that the metes and bounds of the term "nonimmunogenic" are unclear.

Applicants respectfully traverse this rejection. Claim 133 requires administration of peptides in "non-immunogenic ***form***." The meaning of the term "in non-immunogenic ***form***" is not only described in clear detail in Applicants' disclosure, but was also art-recognized at the time of the invention and therefore would have been clear to one of ordinary skill in the art. Evidence of such can be found in numerous references published prior to the filing date of the present application, such as those submitted herewith as Appendices A and B and discussed below.

As disclosed at page 7, lines 7-18, of the specification, stimulation of T cells requires two signals. The first signal is recognition of antigen presenting cells (APCs) by the T-cell receptor (TCR). The second signal is costimulation of T cells by a costimulatory or "second" signal produced by APCs in response to certain auxiliary stimuli, such as adjuvant. Without the occurrence of both T cell epitope recognition and costimulation by APCs, T cells are not stimulated and the various immune responses which normally ensue are not induced. This is believed to be due to the fact that, in the

absence of an agent such as adjuvant which causes APCs to produce the second signal or costimulatory signal, competent APC's are not engaged in the stimulation of appropriate T cells. This can then result in T cell non-responsiveness or reduced T cell responsiveness.

Thus, Applicants disclosure makes it clear that the term "in non-immunogenic form" means in a form which does not include an agent, such as an adjuvant, which induces the co-stimulatory properties of APCs.

The meaning of the term "in non-immunogenic form" was also discussed extensively in the literature at the time the present application was filed. For example, Kearney et al. (1994) *Immunity* 1: 327-339 (Appendix A) teach that "monomeric antigen ***is only immunogenic if injected locally in an adjuvant***" (see page 327) (emphasis added) based on the need for co-stimulation of T cells by APCs. The authors teach that adjuvant "induces local inflammation which enhances the adhesive and costimulatory properties of APC's" (see page 327).

The meaning of administration "in non-immunogenic form" is similarly discussed by Briner et al. (1993) *PNAS* 90: 7608-7613 (Appendix B). Specifically, the authors state that "*in-vivo* tolerance to antigen challenge has been shown using . . . peptides administered in such a way as to preclude the second signal [i.e., co-stimulation by APCs]" (see page 7608). Thus, the art came to know this mode of administration as administration ***in non-immunogenic form***.

Overall, both Applicants' disclosure and the literature at the time of the present invention would have made the metes and bounds of the term "in non-immunogenic form" clear to one of ordinary skill in the art. Based on this, Applicants respectfully request the Examiner to reconsider and to withdraw the rejection.

Rejection of Claims 133 and 103-144 under 35 U.S.C. §112, First Paragraph

The specification stands objected to and claims 133 and 103-144 remain rejected under 35 U.S.C. §112, first paragraph, as failing to adequately describe or enable the claimed invention. The Examiner bases this rejection on the assertion that these claims "encompass use of nonimmunogenic peptides" and that this subject matter is "not described in the specification in such a way as to enable one skilled in the art to which it pertains . . . to make and/or use the invention."

Applicants respectfully traverse this rejection. The Examiner states that "***the peptides used in the claimed methods are immunogenic as they induce immune responses in human patients***" (emphasis added). However, as previously pointed out in response to the rejection under 35 U.S.C. §112, second paragraph, this statement is not entirely correct. T cell epitope containing peptides encompassed by the present claims are ***not*** immunogenic (as defined by T cell stimulation and the occurrence of various ensuing immune reactions such as recruitment of other immune cells, immunglobulins etc.) unless an agent - most commonly adjuvant - is administered along with the peptides to induce the co-stimulatory action of APCs required to cause T cell stimulation.

Therefore, based on the fact that it was well known in the art that T cell epitope containing peptides could be administered in non-immunogenic form ***simply by not including an agent which induces the co-stimulatory action of APCs***, Applicants respectfully submit that the subject matter of claims 133 and 103-144 are fully enabled. Indeed, Applicants' disclosure teaches the most common manner of administering peptides in non-immunogenic, namely by simply omitting any adjuvant (see e.g., page 6, line 27, and page 7, line 15 of the specification). Thus, the disclosure would have fully enabled one of ordinary skill in the art to have made and used (e.g., administered) the peptides encompassed by claims 133 and 1-3-144 without undue experimentation.

Applicants accordingly respectfully request that the rejection be withdrawn.

Rejection of Claims 103-144 Under 35 U.S.C. §103

Claims 103-144 remain rejected under 35 U.S.C. §103 as being unpatentable over Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991) for reasons of record.

Applicants respectfully maintain their traversal of this rejection. The present claims are drawn to a method of treating allergy in humans comprising administration of therapeutic compositions comprising one or more purified (e.g., to at least about 90% purity) T cell epitope containing peptides which have defined amino acid sequences and which are not conjugated to any other molecule. Thus, the compositions encompassed by the present claims provide the distinct advantage of being highly pure and reproducible, making them safer and eminently more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

Sehon et al. teach that conjugation of PEG to peptides can render peptides nonimmunogenic or "tolerogenic." For example, Sehon et al, teach "that the PEG conjugates did not induce anaphylitic death of animals and . . . therefore . . . appear to have the desirable properties of safe immunotherapeutic agents." Thus, the teachings of Sehon et al. would ***not*** have suggested the use of ***unconjugated*** peptides in therapeutic compositions, as claimed by Applicants. In fact, the authors teach directly ***away*** from the use of unconjugated peptides in compositions for human therapy, since they disclose that modification, such as PEG conjugation, is necessary to render the peptides tolerogenic and safe. Moreover as previously pointed out by Applicants, the Examiner agreed during the personal interview that Sehon et al. ***does not teach or suggest the use of a peptide per se or a therapeutic composition containing a peptide.***

Michael et al. also fail to provide any teaching or suggestion which would have led one of ordinary skill in the art to the claimed invention. Michael et al. teach

proteolytic digestion of primary pollen allergens to produce pollen specific polypeptides. Proteolytic digestion of native allergen generates an ***irreproducible*** milieu of polypeptide fragments which have an ***unknown variable composition*** following each digestion. Moreover, not all of the proteolytically digested peptides are certain to contain a T cell epitope. Nor are the peptides highly pure since they are present along with a variety of other contaminating proteins with which the allergen naturally occurs.

In contrast, Applicants claim therapeutic compositions made up of a ***reproducible*** selection of peptides all of which comprise at least one ***T cell epitope*** and which are ***purified to at least about 90%***. Accordingly, based on the teachings of Michael et al., the subject matter presently claimed by Applicants would not have been obvious to one of ordinary skill in the art. Indeed, Micheal et al. fail to provide any motivation at all to have made or used ***highly pure***, ***reproducible*** compositions of T cell epitope containing peptides in human immunotherapy, since they teach that compositions containing proteolytically cleaved allergens, which were known to be easier and less expensive to make, were sufficient for therapy.

Similar to Michael et al., Litwin et al. teach the use of compositions containing native peptic fragments obtained by digestion of chromatographic fractions enriched for ragweed allergen *Amb a* I. Thus, like Micheal et al., Litwin et al. fail to teach or suggest a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides which are ***purified to at least about 90%*** as claimed by Applicants.

Kuo also fails to make up for the many aforementioned deficiencies in the teachings of the above-discussed references. Kuo merely teaches whole *Fel d* I protein modified by treatment with mild base or alkali conditions to reduce IgE reactivity. As previously acknowledged by the Examiner during the personal interview conducted on December 12, 1995, Kuo et al. do not teach or suggest peptides or compositions containing peptides useful for human administration, let alone ***highly pure, reproducible T cell epitope containing peptide compositions***.

In sum, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have made it obvious at the time of the invention to have made or used a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides which are ***purified to at least about 90%,*** as claimed by Applicants. Therefore, Applicants respectfully request the Examiner to reconsider and to withdraw the rejection.

Clarifications Requested by the Examiner

I. At page 9, paragraph (A), of the present Office Action, the Examiner asserts that "it is unclear what encompasses a T Cell Stimulation index."

In response, Applicants respectfully direct the Examiner's attention to page 9, lines 27-35 of the disclosure which reads as follows:

> T cell stimulating activity can be tested by culturing T cells obtained from an individual sensitive to a predetermined protein antigen (i.e. an allergen or an autoantigen) with a peptide derived from the antigen and determining whether proliferation of T cells occurs in response to the peptide as measured, e.g., by cellular uptake of tritiated thymidine. ***Stimulation indices for responses by T cells to peptides can be calculated as the maximum counts per minute (CPM) in response to a peptide divided by the control CPM.*** A T cell stimulation index (S.I.) equal to or greater than two times the background level is considered "positive".

Thus, the body of the disclosure makes it clear what a T cell stimulation index represents, and how to calculate the index.

II. At page 9, paragraph (B), the Examiner asserts that "it is unclear how the term purity is determined" in claims 110, 112, 115-119.

In response, Applicants respectfully direct the Examiner's attention to page 13, line 36, of the disclosure where Applicants teach that purity is determined by a peptide's level of freedom from all other polypeptides and contaminants. In addition, Applicants

teach methods used to characterize purified peptides of the invention at page 14, line 31, to page 15, line 2.

III. At page 9, paragraph (C), the Examiner asserts that "it is unclear by what standard one would measure improvement, e.g., level of mucous secretion, subjective complaints by patients, allergen recovery from nasal mucous."

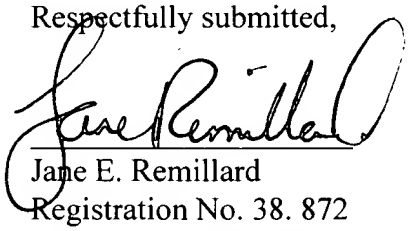
In response, Applicants respectfully direct the Examiner's attention to page 23, line 31, of the disclosure where Applicants teach that improvement is measured by betterment of common allergy symptoms known in the art, such as rhinorrhea, nasal congestion, pruritus, chest tightness, and/or wheezing.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the present application is in condition for allowance.

If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at the number listed below.

Respectfully submitted,



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